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Teaching Point
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Thalidomide: a treatment option for bleeding GI angiodysplasias in dialysed patients

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Introduction

Gastrointestinal (GIT) bleeding is a serious problem in dialysed patients, and can lead to repeated hospitalizations, invasive diagnostic and therapeutic procedures and the need for multiple blood transfusions. Angiodysplasias are the cause of GIT bleeding in 3–6% of all patients [1,2], and in the elderly population they constitute the most common cause for obscure GIT bleeding [3]. As early as 1984, angiodysplasias, often multiple and located throughout the GIT, have constituted a potential source of bleeding in dialysis patients [4].

Today, the ever-increasing use of the wireless capsule endoscope has dramatically improved our ability to accurately diagnose angiodysplasias ([1], Figure 1). Fortunately, many bleeding angiodysplasias stop bleeding spontaneously [2]. But, for those vascular malformations that continue to bleed or bleed recurrently, therapy remains unsatisfactory. Multiple lesions are the rule, rather than the exception. Therefore, surgical resection of any involved segment of the bowel is fraught with the uncertainty of other lesions bleeding at a future point in time. Argon laser coagulation is an accepted mode of therapy, but many angiodysplastic lesions, to be found in the distal small bowel, are 'out of technical reach' of this modality. Medical options have also disappointed, with uncertainty still existing over the use of estrogenic hormones in treating bleeding angiodysplasias [5].

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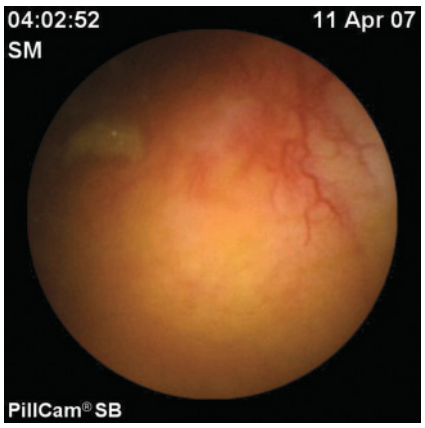

Fig. 1. Caecal angiodysplasia as seen with the wireless capsule endoscope.

Discussion

Angiodysplasias are arteriovenous vascular malformations located on the mucosal and submucosal surfaces of the GIT. Their pathogenesis is still not clear, and probably multifactorial. These malformations are thin-walled, fragile vessels. They lack smooth muscle cells, and are susceptible to rupture [6]. They bleed, often recurrently, and in such a severity, as to require blood transfusions. Vascular endothelial growth factor (VEGF) is an angiogenic peptide that is secreted in response to hypoxia, stimulates proliferation of vascular endothelial cells and increases vessel permeability [7]. GIT angiodysplasias are characterized by elevated serum levels of VEGF [8]. In addition, colonic angiodysplasias stain for both VEGF and basic fibroblast growth factor, another known angiogenic factor, and they also express the VEGF-receptor 1 along their endothelial lining [6]. If suppressing VEGF may lead to a disruption in the pathogenesis behind these pathological vessels, then the use of VEGF suppressive (antiangiogenic) agents may be useful in treating bleeding GIT angiodysplasia. Thalidomide is such a drug [9].

Table 1. Patients' summaries after thalidomide therapy for bleeding angiodysplasias

References	Patient age/sex	Location of angiodysplasia	Blood transfusions	Thalidomide dose and duration of therapy	Immediate result of thalidomide therapy	Long-term results of thalidomide therapy
[1]	Three patients, 2 M, 1 F, mean age: 78 years	NA	≥2 units/month (≥3 months)	50–400 mg, 3–12 months	Two patients stopped bleeding after 2–12 weeks; one patient did not respond	Two patients did not rebleed for 6 months after thalidomide was stopped
[8]	54, M	Small bowel	>200 units (42 months)	100 mg, stopped after 4 months	Bleeding stopped within 2 weeks	No bleeding for 33 months
[8]	69, F	Small bowel	12 units (12 months)	100 mg, stopped after 4 months	Bleeding stopped within 2 weeks	No bleeding for 24 months
[8]	72, M	Jejunum, ileum	>1 unit/month (14 months)	100 mg, stopped after 4 months	Bleeding stopped after 2 weeks	No bleeding for 22 months
[13]	60, F[a]	Stomach, jejunum	8 units/week (8 months)	100–200 mg, 3 months	Decreased blood transfusions (2 units/week)	Died after 3 months (as a result of leukaemia)
[14]	80, M	Duodenum, jejunum	35 units (4 months)	100 mg stopped after 11 months	Bleeding stopped within 1 week, no bleeding for 11 months	Thalidomide cessation led to further episodes of bleeding
[15]	54, M[b]	Stomach, small and large bowel	>130 units (15 months)	50–150 mg, 6 months	Bleeding stopped immediately	No bleeding for 6 months

NA: not available.
[a]This patient had underlying acute myelogenous leukaemia.
[b]This patient had Von Willebrand's disease.

The tragic, early history of thalidomide needs no reintroduction. But, today, thalidomide is an important drug in the management of multiple myeloma and erthyema nodosum leprosy. It possesses anti-inflammatory and anti-angiogenic capabilities [10]. Indeed, D'Amato showed, in an experimental model, that thalidomide is capable of inhibiting VEGF and basic fibroblast growth factor-mediated angiogenesis directly [9]. In gastroenterology, thalidomide was initially used as an anti-inflammatory drug in patients with active Crohn's disease [8,11]. It was quickly recognized that thalidomide stopped GIT bleeding in these same patients. Wettstein *et al*. treated a 55-year-old woman with Crohn's disease and recurrent rectal bleeding with thalidomide, after all other medical therapies had failed. Before commencement of thalidomide this patient had bled incessantly, had been hospitalized on 12 different occasions in 6 months and had required ∼40 blood transfusions. After starting thalidomide, all bleeding stopped within 3 weeks, and bleeding did not recur during a 4-month follow-up period [11]. As GIT bleeding in patients with Crohn's disease is often unrelated to disease activity, it was hypothesized that the anti-angiogenic effects of thalidomide may be the predominant mechanisms behind its ability to stop GIT bleeding [12]. Since then, a number of reports have demonstrated thalidomide's ability to stop angiodysplastic bleeding (Table 1; [1,8,13–15]). In three patients, low-dose thalidomide treatment not only stopped GIT bleeding but also significantly reduced high pre-treatment serum VEGF levels [8]. Furthermore, the serial usage of the wireless capsule endoscope showed that successful therapy with thalidomide led to a decreased size and number of angiodysplasias [3].

In all the reports on thalidomide therapy for GIT bleeding, not even one patient with chronic kidney disease has been included. Also, in a prospective study to be conducted by the Northport Veterans Affairs Medical Center, as to the efficacy of thalidomide in bleeding angiodysplasias, an exclusion criterion is renal failure [16]. But why? Undoubtedly, bleeding GIT angiodysplasias can lead to an increased morbidity and mortality in dialysed patients. Secondly, the only patients who should not use thalidomide are women of child-bearing age, or sexually active men who are not using condom contraception. Thirdly, Eriksson *et al*. have shown that dose adjustment/reduction is not necessary in patients with chronic renal disease or in haemodialysed patients [17]. Therefore, thalidomide should be considered as a viable therapeutic option if the diagnosis of GIT bleeding from angiodysplasias has been made, and especially if other therapeutic options have failed. As Bauditz *et al*. demonstrated in three elderly patients, thalidomide does not have to be maintained for an indefinite period of time [8]. In these patients, low-dose therapy was given for only 4 months, and bleeding did not recur for many months after cessation of thalidomide. Subsequently, this finding was verified in another two patients who required no blood transfusions, for a period of 6 months after thalidomide had been stopped [2].

The main side effects attributable to thalidomide are fatigue, constipation and peripheral neuropathy—all problems that can exist in many dialysed patients. Fatigue can be partially ameliorated by giving the drug at night, before sleep. Constipation can be troublesome, and laxatives should be added whenever needed. Peripheral neuropathy, especially in diabetics, should be looked for at all phases

of therapy, and serial electromyelograms appear warranted. Fortunately, peripheral neuropathy becomes overtly problematic only after high cumulative doses of thalidomide have been given [12].

Bevacizumab, a recombinant humanized monoclonal antibody to VEGF, improved GIT bleeding in a patient with haemorrhagic hereditary telangietasia [18]. However, reports of bowel perforation, following its use in patients with advanced ovarian cancer, means that, as of the moment, this drug cannot be recommended as therapy in angiodysplastic bleeding [19].

Conflict of interest statement. None declared.

References

1. Dabak V, Kuriakose P, Kamboj G *et al*. A pilot study of thalidomide in recurrent GI bleeding due to angiodysplasias. *Dig Dis Sci* 2007
2. Ell C, Remke S, May A *et al*. The first prospective controlled trial comparing wireless capsule endoscopy with push enteroscopy in chronic gastrointestinal bleeding. *Endoscopy* 2002; 34: 685–689
3. Bauditz J, Lochs H, Voderholzer W. Macroscopic appearance of intestinal angiodysplasias under antiangiogenic treatment with thalidomide. *Endoscopy* 2006; 38: 1036–1039
4. Dave PB, Romeu J, Antonelli *et al*. Gastrointestinal telangiectasias. A source of bleeding in patients receiving hemodialysis. *Arch Intern Med* 1984; 144: 1781–1783
5. Junquera F, Fen F, Papo M *et al*. A multicenter, randomized, clinical trial of hormonal therapy in the prevention of rebleeding from gastrointestinal angiodysplasia. *Gastroenterol* 2001; 121: 1073–1079
6. Junquera F, Saperas E, de Torres I *et al*. Increased expression of angiogenic factors in human colonic angiodysplasia. *Am J Gastroenterol* 1999; 94: 1070–1074
7. Ferrera N, Gerber HP, Le Couter J. The biology of VEGF and its receptors. *Nat Med* 2003; 9: 669–676
8. Bauditz J, Schachschal G, Wedel S *et al*. Thalidomide for treatment of severe intestinal bleeding. *GUT* 2004; 53: 609–612
9. D'Amato RJ, Loughnan MS, Flynn E *et al*. Thalidomide as an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994; 91: 4082–4085
10. Tramontana JM, Utaipat U, Molloy A *et al*. Thalidomide treatment reduces tumor necrosis factor α production and enhances weight gain in patients with pulmonary tuberculosis. *Mol Med* 1995; 1: 384–397
11. Wettstein AR, Meagher AP. Thalidomide in Crohn's disease. *Lancet* 1997; 350: 1445–1446
12. Bauditz J, Lochs H. Angiogenesis and vascular malformations: antigiogenic drugs for the treatment of gastrointestinal bleeding. *World J Gastroenterol* 2007; 13: 5979–5984
13. Shurafa M, Kamboj G. Thalidomide for the treatment of bleeding angiodysplasias. *Am J Gastroenterol* 2003; 98: 221–222
14. Heidt J, Langers AMJ, Van Der Meer FJM *et al*. Thalidomide as treatment for digestive tract angiodysplasias. *Nether J Med* 2006; 64: 425–428
15. Hirri HM, Green PJ, Lindsay J. Von Willebrand's disease and angiodysplasia treated with thalidomide. *Hemophilia* 2006; 12: 285–286
16. Northport Veterans Affairs Medical Center. Thalidomide reduces arteriovenous malformation related gastrointestinal bleeding. Clinical trial NCT00389935. http://www.clinicaltrials.gov/ct/gui/show/NCT00389935?order, 2007
17. Eriksson T, Hoglund P, Turesson I *et al*. Pharmacokinetics of thalidomide in patients with impaired renal function, and while on and off dialysis. *J Pharm Pharmacol* 2003; 75: 1701–1706
18. Flieger D, Hainke S, Fischbach W. Dramatic improvement in hereditary hemorrhagic telangiectasia after treatment with the vascular endothelial growth factor (VEGF) antagonist bevacizumab. *Ann Hematol* 2006; 85: 631–632
19. Cannistra SA, Matulonis UA, Penson UA *et al*. Phase II study of bevacizumab in patients with platinum resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol* 2007; 25: 5180–5186

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